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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Paul et al.	§	**ART UNIT: 1652**
FILED: June 1, 2006	§	
SERIAL NO.: 10/581,294	§	**EXAMINER: Meah, M.Y.**
FOR: Proteolytic and Covalent Antibodies	§	**DOCKET: D6812**

ATTN: Group Director Bruce Kisliuk, Group 1600
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF FACSIMILE TRANSMISSION

I certify that this Petition from Requirement for Restriction was transmitted via facsimile to Group 1600 Director Bruce Kisliuk at (571) 273-8300 on the date indicated below:

Date: May 11, 2010

Benjamin Aaron Adler, Ph.D., J.D.

PETITION FROM REQUIREMENT FOR RESTRICTION UNDER 37 C.F.R. §1.144

Dear Sir:

Pursuant to 37 C.F.R. §1.144, Applicants hereby petition from the requirement for restriction of the claims for the above-referenced non-provisional application. Applicants request that the Group 1600 Director consider the following remarks. Reconsideration of the requirement for restriction is respectfully requested.

Respectfully submitted,

Date: May 11 2010

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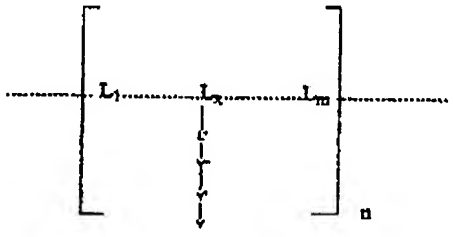
STATUS OF THE CLAIMS

Claim 1 (previously presented): A method of preparing covalent antibodies that that bind a peptide or protein covalently and catalytic antibodies that covalently bind to and hydrolyze the peptide or protein, comprising:

producing in an organism, antibodies to a covalently reactive polypeptide antigen analogue (pCRA) of formula (1):



(1)

wherein, $L_1 \ldots Lx \ldots Lm$ are components defining [[an]] antigenic determinant of the peptide or protein,

Lx is an amino acid residue,

L' is a side chain functional group of Lx,

Y" is or a linker,

Y' is an optional charged or neutral group,

Y is a covalently reactive electrophilic group that reacts specifically with an antibody that binds to said antigenic determinant,

optionally, Y", Y' or Y contains a water-binding group as a terminal or internal component;

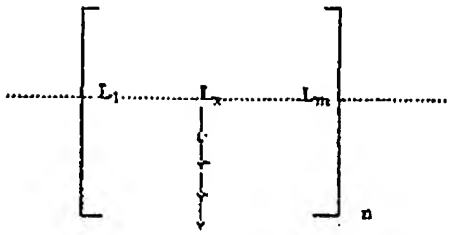
n is an integer from 1 to 1000; and

m is from 4 to 30;

screening and selecting for antibodies that covalently bind to the pCRA or to the peptide or protein having one or more of the antigenic determinant comprising the pCRA to identify covalent antibodies produced in the organism; and

screening and selecting for antibodies that covalently bind to the pCRA and screening from among the covalently binding antibodies for antibodies that catalytically hydrolyze a peptide bond in the peptide or protein having the antigenic determinant comprising the pCRA to identify catalytic antibodies produced in the organism, thereby preparing covalent antibodies and catalytic antibodies.

Claim 2 (withdrawn and previously presented): A water-binding, covalently reactive polypeptide antigen analogue (pCRAW) of formula (1):



(I)

wherein, L_1 . . . Lx . . . Lm are components defining an a polypeptide antigenic determinant of the peptide or protein,

Lx is an amino acid residue,

L' is a side chain functional group of Lx,

Y" is or a linker,

Y' is an optional charged or neutral group,

Y is a covalently reactive electrophilic group that reacts specifically with an antibody that binds to said antigenic determinant,

Y", Y' or Y contains a water-binding group as a terminal or internal component;

n is an integer from 1 to 1000; and

m is from 4 to 30.

Claim 3 (withdrawn): The pCRAW of claim 2, wherein the water-binding group is composed of a site that binds a metal ion which chelates one or more water molecules.

Claim 4 (withdrawn): The pCRAW of claim 3, in which the metal is zinc, copper, nickel, cobalt, calcium or magnesium.

Claim 5 (withdrawn): The pCRAW of claim 2, in which the metal binding group is selected from: -(His).sub.n- where n=2 or more, -Cys-X-Cys-Cys- or -Cys-X-Cys- wherein X is an amino acid residue, ethylene diamine tetraacetic acid or diaminomethyl pyridine.

Claim 6 (previously presented): The method of claim 1, wherein binding of the covalent and catalytic antibodies to the peptide or the protein is resistant to dissociation by a denaturant that disrupts non-covalent antigen binding.

Claim 7 (previously presented): The method of claim 1, wherein the binding of the covalent and catalytic antibodies to the peptide or the protein is resistant to dissociation by 2% sodium dodecyl sulfate.

Claim 8 (previously presented): The method of claim 1, wherein the protein is HIV-1 gp120.

Claims 9-10 (canceled)

Claim 11 (previously presented): The method of claim 1, wherein the covalent antibodies or catalytic antibodies are polyclonal antibodies identified in the serum of said organism.

Claim 12 (previously presented): The method of claim 1, wherein the antibodies are monoclonal antibodies or antibody fragments obtained from lymphocytes of said organism; wherein the steps of screening and selecting further comprise:

a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes expressed from a vector prior to screening and selecting for the covalent antibodies and the catalytic antibodies or antibody fragments thereof; and

b) purifying the covalent antibodies and catalytic antibodies or the antibody fragments thereof.

Claim 13 (previously presented): The method of claim 1[[2]], in which the antigenic determinant of the pCRA is ~~the CRA derivative of~~ comprises gp120, VIP, Factor VIII, epidermal growth factor receptor, CD4, β-amyloid peptide 1-40, or β-amyloid peptide 1-42.

Claim 14 (canceled).

Claim 15 (previously presented): The method of claim 12, wherein the organism is a transgenic mouse expressing human antibody genes.

Claim 16 (original): The method of claim 12, wherein the organism is a mouse.

Claim 17 (original): The method of claim 12, wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

Claim 18 (previously presented): The method of claim 1, wherein the antibody fragments are single chain Fv fragments obtained by steps comprising:

a) preparation of the immunoglobulin VL and VH cDNA by reverse-transcriptase polymerase chain reaction;

b) cloning the VL and VH cDNA in a vector in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector; and

c) contacting the vector particles with inmmobilized pCRA of claim 1, removal of unbound vector particles by washing, and expression of the Fv genes from the pCRA-bound vector particles in soluble form in prokaryotic or eukaryotic cells.

Claim 19 (original): The method of claim 12, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA from lymphocytes that are not bound to the pCRA.

Claim 20 (canceled).

Claim 21 (original): The method of claim 1, wherein the antibodies belong to the IgG, IgM, IgD, IgA or IgE classes.

Claim 22 (original): The method of claim 1, wherein the antibodies are fragments of IgG, IgM, IgD, IgA or IgE.

Claim 23 (original): The method of claim 1, wherein [L_1 . . . Lx . . . Lm] represents an antigenic determinant of a microbial protein.

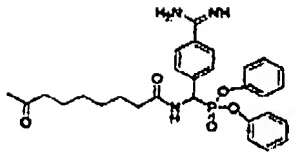
Claim 24 (canceled).

Claim 25 (original): The method of claim 1, wherein [L_1 . . . Lx . . . Lm] represents an antigenic determinant of a human, animal or plant protein.

Claims 26-28 (canceled).

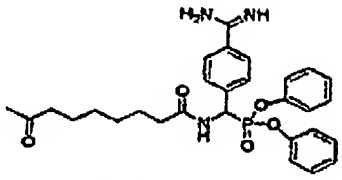
Claim 29 (original): The method of claim 1, wherein n is from 1 to 23.

Claim 30 (original): The method of claim 1, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:

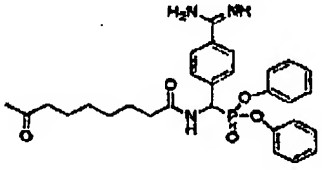


Claim 31 (canceled).

Claim 32 (original): The method of claim 1, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with:



Claim 33 (previously presented): The method of claim 1, wherein the antigenic determinant is derived from the soluble extra-cellular domain of epidermal growth factor receptor, soluble extra-cellular domain of CD4, Factor VIII, .beta.-amyloid peptide 1-40 or .beta.-amyloid peptide 1-42, each derivatized at Lys side chains with:



Claim 34 (withdrawn and previously presented): The method of claim 12, wherein the monoclonal IgG antibody clones YZ-18, YZ-20 and YZ-24 that catalyze the cleavage of gp120.

Claim 35 (withdrawn and previously presented): The method of claim 12, wherein the monoclonal IgG antibody clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind the gp120-CRA of claim 30 and the binding is resistant to dissociation with 2% SDS.

Claim 36 (withdrawn and previously presented): The method of claim 12, wherein the monoclonal IgG antibody clones YZ-18, YZ-19, YZ-20, YZ-21, YZ-22, YZ-23 and YZ-24 that bind gp120 and the binding is resistant to dissociation with 2% SDS.

Claim 37 (withdrawn and previously presented): The method of claim 12, wherein full-length IgG, IgM and IgA antibodies are prepared from the antibody fragments, by steps comprising:

a) insertion of the VL and VH domain cDNA at the 5' side of Ig constant domains contained in an expression vector by nucleic acid digestion and ligation procedures;

b) growth of the vector in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

Claim 38 (withdrawn and previously presented): A method of obtaining monoclonal covalent antibodies, catalytic antibodies, covalent antibody fragments or catalytic antibody fragments from the lymphocytes of organisms with autoimmune disease, organisms with autoimmune disease, organisms without known disease or transgenic mice expressing human antibody genes comprising the steps:

a) preparing a library of hybridoma cell lines, virus-transformed cell lines or immunoglobulin fragment genes cloned in and expressed from a vector;

b) screening and selection for covalent activity of antibodies or antibody fragments by binding to an antigenic pCRA of claim 1 or a polypeptide;

c) screening and selection for catalytic hydrolysis of a polypeptide by the antibodies or antibody fragments; and

d) purifying the antibodies or the antibody fragments.

Claim 39 (canceled).

Claim 40 (withdrawn): The method of claim 38, wherein the antibodies hydrolyze peptide bonds in superantigenic polypeptides.

Claim 41 (withdrawn): The method of claim 38, wherein the antibodies hydrolyze gp120.

Claim 42 (withdrawn): The method of claim 38, wherein the antibodies hydrolyze CD4.

Claim 43 (withdrawn): The method of claim 38, wherein the antibodies hydrolyze .beta.-amyloid peptides.

Claim 44 (canceled).

Claim 45 (withdrawn): The method of claim 38, wherein the autoimmune disease is systemic lupus erythematosus.

Claim 46 (withdrawn): The method of claim 38, wherein the immunoglobulin fragments are the VL and VH domains linked by a peptide linker.

Claim 47 (withdrawn): The method of claim 38, wherein the immunoglobulin fragments are the light chain subunits.

Claim 48 (withdrawn): The method of claim 38, wherein the vector is selected from the group consisting of phage display vectors, retroviral display vectors, yeast display vectors, bacterial display vectors and mammalian display vectors.

Claim 49 (canceled).

Claim 50 (withdrawn): The method of claim 38, wherein the antibody fragments are single chain Fv fragments or light chains expressing covalent or catalytic activity isolated by steps comprising:

a) preparing the immunoglobulin VL cDNA, VH cDNA and light chain cDNA by reverse-transcriptase polymerase chain reaction using as template the RNA from lymphocytes;

b) cloning the VL and VH cDNA in a form enabling their expression as single chain Fv fragments expressed on the surface of a display vector;

c) cloning the light chain cDNA in a vector in a form enabling their expression as light chains expressed on the surface of a display vector;

d) contacting the vector particles with immobilized pCRA of claim 1, removal of unbound vector particles by washing, and expressing the Fv cDNA or light chain cDNA from the pCRA-bound vector particles in soluble form in prokaryotic or eukaryotic cells;

e) screening the soluble Fv or light chain constructs for covalent antigen binding activity;

f) screening the soluble Fv or light chain constructs for catalytic activity.

Claim 51 (withdrawn and previously amended): Full-length IgG, IgM and IgA antibodies prepared from the Fv fragments of claim 50 prepared by steps comprising:

a) insertion of the VL and VH: domain cDNA at the 5' side of Ig constant domains contained in an expression vector by nucleic acid digestion and ligation procedures;

b) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

Claim 52 (withdrawn and previously presented): Full-length IgG, IgM and IgA antibodies prepared from the light chain fragments of claim 50 prepared by steps comprising:

a) insertion of the light chain cDNA into an expression vector by nucleic acid digestion and ligation procedures;

b) insertion of the VH domain of gp120 binding antibodies at the 5' side of an IgG heavy chain constant domain contained in an expression vector by nucleic acid digestion and ligation procedures;

c) growth of the vectors in a prokaryotic or eukaryotic host cell, extraction of the full-length antibodies from the culture medium or the cellular contents and purification of said antibodies.

Claim 53 (withdrawn): The method of claim 38, wherein lymphocytes are obtained by steps comprising:

a) contacting the lymphocytes with a pCRA;

b) separating lymphocytes that are bound to the pCRA firom lymphocytes that are not bound to the pCRA.

Claim 54 (canceled).

Claim 55 (withdrawn): The method of claim 38, wherein the antibodies belong to the IgG, IgM, IgD, IgA or IgE classes.

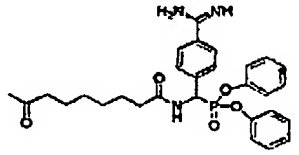
Claim 56 (withdrawn): The method of claim 38, wherein [L_1 . . . Lx . . . Lm] in the pCRA represents an antigenic determinant of a microbial protein.

Claim 57 (withdrawn): The method of claim 38, wherein [L_1 . . . Lx . . . Lm] in the pCRA represents an antigenic determinant of the HIV-1 protein.gp120.

Claims 58-61 (canceled).

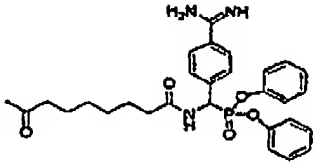
Claim 62 (withdrawn): The method of claim 38, wherein n is from 1 to 23.

Claim 63 (withdrawn): The method of claim 38, wherein the pCRA is gp120 derivatized at the Lys side chain amino groups at a density of 23 moles/mole protein with:

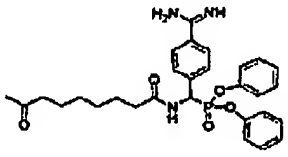


Claim 64 (canceled).

Claim 65 (withdrawn): The method of claim 38, wherein the pCRA is vasoactive intestinal peptide derivatized at the Lys20 side chain with:



Claim 66 (withdrawn): The method of claim 38, wherein the immunogenic determinant is derived from the soluble extra-cellular domain of the epidermal growth factor receptor, soluble extra-cellular domain of CD4, Factor VIII, .beta.-amyloid peptide 1-40 or .beta.-amyloid peptide 1-42, each derivatized at Lys side chains with:



Claim 67 (withdrawn): A method to improve the covalent or catalytic activity of the antibody fragments of claim 12, comprising the steps:

a) introducing mutations in the VL and VH domains;

b) display of the resultant antibody fragments on the surface of a display vector;

c) contacting the vector particles with the pCRAW, and removal of unbound vector particles

d) expressing the antibody fragments in soluble form in prokaryotic or eukaryotic cells;

d) screening the antibody fragments for covalent antigen binding activity;

e) screening the antibody fragments for catalytic activity.

Claim 68 (canceled).

Claim 69 (withdrawn): A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity specific for an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 1; and

b) repeating step a) as necessary for maintenance therapy.

Claim 70 (withdrawn): A method for passive immunotherapy of a disease, comprising:

a) administering a therapeutically effective amount of antibodies having covalent or catalytic activity specific for an antigen associated with a medical disorder in the patient, said antibody having been produced by the method of claim 38; and

b) repeating step a) as necessary for maintenance therapy.

Claim 71 (original): The method of claim 1, wherein the antibody is directed to gp120 for immunotherapy of HIV-1 infection.

Claims 72-75 (canceled).

Claim 76 (withdrawn): A method for stimulating production of prophylactic antibodies in an organism, having covalent or catalytic activity specific for an antigen associated with a medical condition in the organism, comprising the steps of:

a) administering to an organism a vaccine containing an immunogenic amount of a pCRA prepared from said antigen as of claim 1;

b) repeating step a) as necessary to ensure effective antibody production.

Claim 77 (withdrawn): The method of claim 76, in which the medical disorder is a microbial disease and the pCRA is prepared from a constituent protein of the microbe.

Claim 78 (withdrawn): The method of claim 77, in which the medical disorder is HIV-1 infection and the pCRA is prepared from gp120.

Claim 79 (withdrawn): A method of treating a medical disorder in a patient by inhibiting the action of a catalytic antibody, comprising the steps of:

a) administering to said patient a therapeutic amount of a pCRA in which the antigenic determinant is derived from an epitope irreversibly bound by said catalytic antibody;

b) assessing said patient for inactivation of said catalytic antibody; and

c) repeating step a) as necessary to maintain inhibition of said action of said catalytic antibody.

Claim 80 (withdrawn): The method of claim 79, wherein said disease state is an autoimmune disease.

Claim 81 (canceled).

Claim 82 (withdrawn): The method of claim 79, wherein said medical disorder is a lymphoproliferative disorder.

Claim 83 (withdrawn): The method of claim 82, wherein said lymphoproliferative disorder is selected from the group consisting of multiple mycloma, acute lymphoblastic leukemia, lymphoblastic lymphoma, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, Waldenstroms macroglobulinemia, follicular center lymphoma, mucosa-associated lymphoid tissue lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, Burkitts lymphoma, and node based moncocytoid lymphoma.

Claim 84 (withdrawn): The method of claim 12, wherein the organism expresses a genetic defect resulting in defective B cell receptor mediated transmembrane signaling in B cells.

Claim 85 (withdrawn): The method in claim 84, in which the defective B cell receptor mediated transmembrane signaling is caused by altered expression of CD19, CD22 or Lyn.

Claim 86 (new):The method of claim 1, wherein Y'', Y' or Y contains a water-binding group as a terminal or internal component.

Claim 87 (new): The method of claim 86, wherein the water-binding group is composed of a site that binds a metal ion which chelates one or more water molecules.

Claim 88 (new): The method of claim 87, in which the metal is zinc, copper, nickel, cobalt, calcium or magnesium.

Claim 89 (new): The method of claim 87, in which the metal binding group is selected from: -(His).sub.n- where n=2 or more, -Cys-X-Cys-Cys- or -Cys-X-Cys- wherein X is an amino acid residue, ethylene diamine tetraacetic acid or diaminomethyl pyridine.

REMARKS

Applicants submit the following petition under 37 C.F.R. §1.144 from the requirement for restriction of the claims for the above-referenced non-provisional application and respectfully request that Group 1600 Director, Bruce Kisliuk consider the following remarks in support of Applicants' petition. Reconsideration of the restriction requirement is respectfully requested.

The Examiner issued a Restriction Requirement on May 2, 2008 restricting the claims into 32 groups under PCT Rule 13.1. The Examiner stated:

> "The inventions listed in Groups 1-32 do not relate to a single general inventive concept under PCT Rule 13.1, because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature linking groups 1-32, pCRA antigen, does not constitute a "special technical feature" as defined by PCT Rule 13.2 because it does not claim a feature which defines a contribution over the prior art as said antigen is taught by Taguchi et al. (Biorg Med. Chem, 2002, 12:3167-3170)."

Applicants provisionally elected Group 1, claims 1, 6-33, 71-75 and traversed both the requirement for election of claims and the requirement for the election of a species for component "L" in the Group I claims.

In traversing the requirement, Applicants responded that the special technical feature linking Groups 1-32 is the conformational flexibility of the pCRA and pCRAW antigens. Applicants stated that this unifying special technical feature is essential for coordinated alignment of the electrophilic and noncovalent binding sites of the antigens, respectively, with the complementary nucleotphilic and noncovalent binding sites of the antibody (PP 0010). Applicants pointed out that Taguchi et al. do not teach this unifying special technical feature, but rather teach only a small peptide antigen in which the electrophile is located at the C terminus, a location that does not allow optimally coordinated alignment between the interacting subsites of the antigen and antibody. The conformational flexibility disclosed in the instant invention allows new and improved pCRA and pCRAW antigens corresponding to a varied group of large and small molecules, including antigens containing an amino acid, a sugar residue, a fatty acid residue, or a nucleotide.

Applicants maintained that the inventive concept in the claims restricted into Groups 1-32 is that the Y'-Y"-Y component contains a flexible electrophile Y that forms a full or partial covalent bond with the nucleophile of the antibody and the antigenic determinant. Thus, the identity and structure of the noncovalent binding site in the antigenic determinant can be changed at will without compromising the inventive concept. The ligand components L1...Lx...Lm and Lx-L' simply identify components of the antigenic determinant available for noncovalent binding, no matter whether these components are composed of amino acids, sugars, fatty acids, or nucleotides. Applicants concluded that a prior art

search would necessitate searching the electrophilic Y'-Y"-Y component regardless of the structure of L1...Lx...Lm and Lx-L' and requested the rejoinder of Groups 1-32 and the examination of claims 1-85.

In the Office Action mailed January 30, 2009, the Examiner maintained that claims 1-85 are not linked by a special technical feature because of the disclosure in Taguchi et al. In support of his position, in a 35 U.S.C. §102(a) rejection of claims 1, 8-14, 16, 24, and 31, the Examiner stated that

> "**Taguchi** et al teach catalytic antibody raised by using gp120 polypeptide epitope (L of claim 1 having carboxyl functional group of amino acid residue as "Y") attached covalently to phosphonate ester (Y reactive electrophilic group, Transition state analogue) which comprise covalently reactive antigen (PCRA [sic]) (page 3168 fig 1) and wherein said phosphonate ester moiety bind to the antibody and method of producing said antibody by inducing said PCRA to mouse (page 3168, column 1, pargh. 3). "

The Examiner concluded that claims 2-5, 34-70 and 76-85 remain withdrawn and that the restriction is maintained and made FINAL (Examiner's emphasis).

In their response, Applicants amended the claims to limit the antigenic determinant L1...Lx...Lm of the pCRA to peptide or protein and to clarify that L' is a side chain functional group of the amino acid Lx. Applicants argued that the prior art does not teach this unifying special technical feature even in view of the amendments to the pCRA structure. Applicants maintained that Taguchi et al is restricted to a small peptide antigen in which the electrophile is located at the C-terminus. Positioning the small peptide antigen at the C terminus does not allow optimal coordinated alignment between the interacting subsites of antigen and antibody. Applicants reiterated that the inventive concept in the claims identified in Groups 1-32, in distinct contrast to that in Taguchi et al., is that the Y'-Y"-Y' component contains a flexible electrophile Y that forms a full or partial covalent bond with the nucleophile of the antibody as defined in Paragraph 0087 of the instant specification. The reaction is coordinated with non-covalent binding between the antibody and the antigenic determinant.

In rebuttal to the Examiner's contention that Taguchi et al. teach Applicants' pCRA, Applicants emphatically stated that the CRA in Taguchi et al. is distinctly not identical to the pCRA/pCRAW in Applicants' claims. In support of this position, Applicants noted initially that the CRA of **Taguchi** et al. is limited to a single electrophilic antigenic epitope within a small peptide produced by peptide synthesis. The genus of pCRAs in the present invention includes large proteins containing many electrophilic epitopes, in which the electrophile is attached to individual epitopes on the side chains of various amino acids. Applicants submitted that one skilled in the art would be aware that large proteins cannot be synthesized by purely chemical synthetic methods. Moreover, Applicants state that it is not possible to produce the post-translationally modified versions of native proteins by chemical synthetic means. In contrast, pCRAs can be prepared by modification of proteins that have been assembled by natural means, e.g., proteins purified from blood or from supernatants of cultured cells. Therefore, the pCRAs have substantially greater utility than the peptidyl phosphonate ester taught by **Taguchi** et al.

Applicants' second point was that the teaching of **Taguchi** et al. is limited to a linear electrophilic epitope composed of contiguous amino acids. The genus of pCRAs in the present invention includes conformational (discontinuous) electrophilic epitopes composed of spatially neighboring amino acids that are distant from each other in the linear sequence (represented as L1...Lx...Lm in the pCRA formula). For one skilled in the art, it is clear that the vast majority of antigenic epitopes in proteins are conformational epitopes. Therefore, the pCRAs have substantially greater utility than the peptidyl phosphonate ester taught by **Taguchi** et al.

Applicants' third point was that **Taguchi** et al. teach only a peptidyl phosphonate ester containing the electrophilic group located at the C terminus of the peptide. **Taguchi** et al. does not teach incorporation of the electrophilic group in a side chain functional group of the amino acids of a polypeptide. This is a central difference enabling the pCRA technology. One skilled in the art is aware that incorporation of the electrophilic group in the side chain of one or more amino acids within the polypeptide or in the side chain of the N and C terminal amino acids is readily attainable. In contrast, **Taguchi et al** teaches incorporation of the electrophilic group at the C terminal carboxyl group of a small peptide by total chemical synthesis. As described in the foregoing remarks, it is not possible to prepare large proteins with an electrophilic group at the C terminus by total chemical synthesis. Applicants reiterated that the structure of the peptidyl phosphonate ester taught by **Taguchi et al** is not described by the formula of pCRA stated in amended claim 1 wherein L' is a side-chain functional group of Lx. Therefore, the basis for the Examiner's restriction of claims 1-85 is not proper and Applicants again requested that the claims be rejoined.

However, in the Office Action mailed October 28, 2009, the Examiner maintained the restriction of the claims so that claims 2-5, 34-70 and 76-85 remain withdrawn. The Examiner rejected the Applicants' contention that the original claims are unified by several technical features as described at length in Applicants' submission of July 30, 2009. Specifically, the Examiner stated

> "As explained before in the election/rejection office action 05/02/2008, claims are not linked by a special technical feature because the prior art (Taguchi et al. Biorg Med. Chem. 2002, 12:3167-3170) teaches applicants' covalently reactive polypeptide antigen pCRA (CRA of Taguchi et al). Applicants' argument about conformational flexibility of polypeptide covalently reactive antigen (pCRA) molecule is considered but found to be unpersuasive. Conformational flexibility of the pCRA and CRA antigens is not considered a special technical feature, because the art teaches all the structural limitations of the pCRA antigen as well as the method of claim 1 as evidenced by the teachings of CRA of Taguchi et al. Therefore, the pCRA antigen of claim 1 has the "conformational flexibility" by virtue of having the recited structure, and since Taguchi et al. teach a CRA antigen having that same structure, Taguchi et al. teach this "conformational flexibility" technical feature."

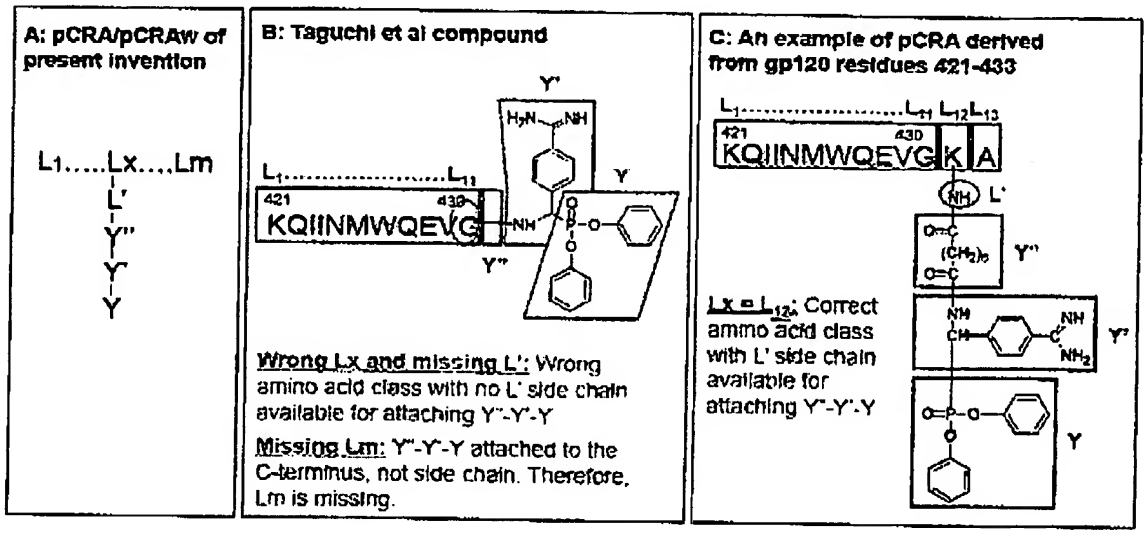
Prior to submitting a response to the Office Action, Applicants and the undersigned Attorney of Record had a telephone interview with Examiner Meah on October 30, 2009 to emphasize, inter alia, that Taguchi et al. does not teach Applicants' pCRA or pCRAW and, therefore, cannot teach the unifying special technical feature of conformational flexibility provided by Applicants' pCRA and pCRAW. However, as indicated in the subsequent Interview Summary, the Examiner disagreed and recommended that Applicants amend the claims around the prior art.

Although in their Response submitted April 28, 2010, Applicants amended the pCRA/pCRAW structures of claim 1 and withdrawn claim 2 to limit the Y" component to a linker and to overcome a 35 U.S.C. §112, second paragraph, rejection for indefiniteness in the recitation of "covalent antibodies" and "catalytic" antibodies", Applicants state that these amendments do not affect their previous arguments that the conformationally flexible Y"...Y"...Y electrophile bound to the L' side chain functional group is the unique special technical feature of the claims and that Taguchi et al. teach neither this technical feature nor Applicants' pCRA structure.

In their response, Applicants strongly averred that the pCRA of the instant amended independent claim 1 (and the pCRAW of amended withdrawn claim 2) and the conformational flexibility resulting from the structural arrangement provide the unifying feature of the claims. In their arguments Applicants submitted **Taguchi** *et al.*, the pCRA (and the pCRAW) are not identical to the CRA of **Taguchi** *et al.* Specifically, *inter alia*, the electrophile in the CRA of **Taguchi** et al. is not located at the functional group of an amino acid as in Applicant's pCRA. In contrast, the electrophile of Taguchi et al is located at the C terminus. Moreover, the CRA of Taguchi et al does not contain a linker between the electrophile and the peptide C terminus. Without the linker, the electrophile in **Taguchi** et al. does not possess the requisite conformational flexibility provided to the electrophile in the instant pCRAs and pCRAWs. It is the pCRA (and pCRAW) structure, including the greater degree of conformational flexibility conferred by the combined side chain functional group-linker-electrophile unit, per se that is the unifying element in claims 1-85.

Applicants provided even more detailed arguments demonstrating that Taguchi et al. do not teach Applicants' pCRA or pCRAW and, therefore, cannot teach Applicants' special technical feature of the flexible Y"...Y'...Y electrophile. At a minimum Applicants submitted that the CRA of **Taguchi** *et al.* does not have a Y" group as in Applicants' claim 1. Applicants presented the diagram below to explain their position. Panel (A) shows the general formula for pCRAs of the present invention. Panel (B) shows the compound disclosed in **Taguchi** *et al*, an analog of gp120 residues 421-433. This compound consists of a peptide corresponding to residues 421-431, in which the backbone carboxyl group of Gly431 is connected to the aminoalkylphosphonate group via a C-N covalent bond. The chemical designation system identifying the pCRA elements in the present invention is employed to identify various components of the **Taguchi** *et al* compound. Panel (C) shows an example pCRA of the present invention corresponding to gp120 residues 421-433. Element Lx in the **Taguchi** compound is devoid of a side chain and cannot be used prepare a pCRA of the present invention, as a defining feature of the pCRAs is

the side chain location of the unit composed of elements L'-Y"-Y-Y. Moreover element L' of the present invention is missing altogether in the **Taguchi** *et al* compound. Also, element Lm is also missing in **Taguchi** et al compound, as the unit composed of elements Y"-Y'-Y is attached to the C-terminus. In comparison, the unit of elements Y"-Y'-Y is attached to the side chain in the pCRAs, making possible incorporation of element Lm in the present invention. Thus, the lack of chemical identity between the **Taguchi** *et al* compound and the pCRAs of the present invention is evident.



Therefore, Applicants respectfully requested that withdrawn claims 2-5, 34-38, 40-43, 45-48, 50-53, 55-57, 62-63, 65-70 76-80, and 82-85 be rejoined with the examined claims, as Applicants have canceled claims 39, 44, 49, 54, 58-61, 64, and 81 and that new claims 86-89 be joined with the examined claims. Applicants requested that new claims 86-89 be examined since they narrow the structure of the pCRA of amended claim 1.

Particularly, Applicants drew the Examiner's attention to claims 2-5 which encompass the pCRA structure of claim 1 including the optional water-binding group recited in claim 1.

Also, Applicants particularly pointed out to the Examiner that withdrawn claim 38 depends indirectly from examined claim 1 via examined claim 12 and recites a method for preparing the antibodies using the pCRA of claim 1 in an organism with autoimmune disease by the method steps recited in original pending claim 12. Applicants noted that claims 34-36 were amended to depend from claim 12 and that claims 67, 84-85 depend directly or indirectly from claim 12 as originally filed. Applicants also noted that claims 40-43, 45-48, 50-53, 55-57, 62-63, 65, 68, and 70 depend directly or indirectly from claim 38.

In addition, Applicants particularly pointed out to the Examiner that claim 76 depends directly from examined claim 1 and recites a method for preparing the antibodies using the pCRA of claim

1 in an organism with a medical condition, etc. by the method steps recited in original pending claim 1. Applicants noted that claims 77-78 depend directly or indirectly from claim 76.

Furthermore, Applicants particularly pointed out to the Examiner that claims 79-80, 82 and 84 utilize the pCRA in methods of treating medical conditions, such as autoimmune diseases. Thus, practice of the methods recited in the withdrawn claims all require the pCRA of amended independent claim 1.

Applicants submit that the arguments presented in the previous responses discussed supra amply demonstrate that basing a requirement for restriction on Taguchi et al. is improper. Accordingly, in view of these arguments, Applicants respectfully petition that the requirement for restriction of the claims be reconsidered. Applicants submit that this petition is complete. If any issues remain outstanding, please telephone the undersigned attorney of record for resolution. Applicants believe that no fees are due, however, should this be in error, please debit any applicable fees from Deposit Account No. 07-1185, upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: May 11, 2010

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